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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	11

DATE MAILED: 02/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/848,868	IVERSEN ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *8-17,19-22 and 34-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,23-33 and 38* is/are rejected.

7)☒ Claim(s) *18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group VIII in Paper No. 9 is acknowledged.

Applicant's election with traverse of SEQ ID NO: 35 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the examination of two sequences does not pose an undue burden, particularly since both sequences target p53, and that MPEP 803.04 states that up to ten sequences would be considered reasonable. This is not found persuasive because a search of more than one (1) of the antisense sequences claimed presents an undue burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed antisense sequences. Further, although they both target the same gene, SEQ ID NO: 35 and 36 are considered to be unrelated, since each antisense sequence claimed is structurally and functionally independent and distinct for the following reasons: each antisense sequence has a unique nucleotide sequence, each antisense sequence targets a different and specific region of the p53 gene, and each antisense, upon binding to the p53 gene, functionally modulates the expression of the p53 gene to a varying degree.

The requirement is still deemed proper and is therefore made FINAL.

Claims 8-16, 19-22 and 34-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there

being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9.

Claims 1-7, 18, 23-33 and 38 will be examined to the extent that they read on the elected subject matter, antisense complementary to a target region of a pre-processed mRNA encoding p53.

Claim Objections

Claims 2, 3, 25 and 26 are objected to because of the following informalities: Reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim" See MPEP 2173.05(s). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 25 are indefinite because they reference structures presented in Figures 2AA-2EE, these structures include variables that have not been defined, for example, X, Y, Z, R and R', and, therefore, the structures

encompassed in the claims is undefined. Claims 3 and 26 are dependent from claims 2 and 25, respectively, but are not rejected under these grounds because these variables have been defined in claims 3 and 26.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 23-33 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification discloses SEQ ID NO: 35 and 36 which correspond to antisense complementary to a target region of a nucleic acid encoding p53 wherein the 5' end of the target region is 1-25 bases downstream of a splice acceptor site at the exon 2 splice junction of human p53. SEQ ID NO: 35 and 36 meet the written description provisions of 35 USC 112, first paragraph. However, claims 1-7 and 23-33 are directed to encompass antisense complementary to a target region wherein the 5' end of the target region is 1-25 bases downstream of any normal splice acceptor site, which would include cryptic splice sites. Antisense complementary to these target regions do not meet the written description provision of 35 USC 112, first paragraph. The specification provides

consensus sequence to identify splice acceptor sites in yeast and human RNA (see page 11), however, these consensus sequences are not absolute, for example, the mammalian consensus sequence has one invariable A residue at the branch point, an AG site located at a variable length from the A and all other residues are only vaguely defined. The yeast consensus is more well defined, but still highly variable. The specification has defined the sequence of one target region (SEQ ID NO:36) at one splice acceptor site in one p53 mRNA, but has not provided the location of other splice acceptor sites, or the structure (ie. sequence) of the down stream target region of such sites. The skilled artisan would not recognize that the inventors had possession of antisense targeted to other downstream regions within the human p53 mRNA, or to regions downstream of acceptor sites within other p53 mRNA's, because the specification does not describe the location and sequence of the splice acceptor sites within these mRNA. The consensus sequences are not sufficient to describe these acceptor sites because the consensus sequences are vague and highly variable. The specification has not described which sites within p53 mRNA's fit these consensuses sequences and actually act as splice acceptors. The specification provides insufficient written description to support the genus encompassed by the claim, because the claims antisense encompass a broad genus of sequences, targeted to regions throughout nucleic acids encoding p53, with variable sequences, targeted to splice acceptors sites which are also highly variable.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO: 35 and 36, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required.

Therefore, only SEQ ID NO: 35 and 36 but not the full breadth of the claim meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision.

Claims 23-33 and 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 23-33 and 38 are drawn to methods of inhibiting normal splicing of p53 mRNA in a eukaryotic cell by contacting the cell with an uncharged

morpholino antisense compound that hybridizes to the target mRNA at a target region with a 5' site within 1-25 bases of a splice acceptor site, wherein the mRNA splices at an alternative site to produce a truncated coding sequence. These methods are further drawn to methods wherein the antisense comprises particular modifications and comprises SEQ ID NO:35. The specification contemplates use of these methods in cells in vivo (whole organism) and wherein the methods are used for therapeutic purposes (see for example, page 27 of the specification).

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are drawn broadly to encompass inhibition of normal splicing in generally any eukaryotic cell, in vivo (whole organism) or in vitro (cell culture), using antisense targeted to a region with a 5' start at 1-25 bases of any splice acceptor site in a p53 mRNA. These claims would also broadly encompass therapy for generally any p53-associated disease. p53 is a tumor suppressor protein involved in more than half of all human cancers (see for example Boeke et al. US Patent No. 6,183,964, Background of the invention, column 1) and is also a transcription factor that regulates a large number of genes (see for example Levine et al. US Patent no. 6,171,798, column 1, background of the

invention) and, therefore, changes in p53 expression and splicing would have a broad impact in cells in an organism.

The specification describes one splice acceptor region to target with antisense in the human p53 gene (SEQ ID NO:36) and describes one particular antisense for that site that would be expected to interfere with exon 2 splicing and translation at the AUG start site. The specification describes potential cryptic splice sites, expected to produce a truncated coding region, associated with this one site. The claimed methods require that the outcome of this alternative splicing produces a truncated coding sequence, rather than a nonsense transcript, however, there is no description provided for other splice sites and cryptic splice sites within the human p53 gene, or other eukaryotic p53 mRNA's, such that the skilled artisan could determine what regions to target with antisense and what particular antisense within that target region would result in a truncated form of p53, rather than inhibiting p53 expression or producing a nonsense transcript, for example, although the specification indicates that truncation competent splice sites exist down stream of the regions targeted by SEQ ID NO:35, secondary structure in this region my result in alternative splicing at a nonsense splice site, sequences near a particular site may act as a splice enhancer causing a nonsense acceptor site to be favored over a truncation site or SEQ ID NO:35 may act as a traditional antisense, inhibiting expression altogether, given the proximity to the translation start site. The specification has not provided any examples of methods wherein antisense targeted to p53 at a region starting 1-25 bases downstream of a splice acceptor site is used to inhibit

normal p53 splicing, producing a truncated p53 protein, in eukaryotic cells in vitro(cell culture) or in vivo(whole organism). The specification has not provided any examples wherein an antisense molecule targeted to p53 is delivered to eukaryotic cells in vivo (whole organism) and a truncated form of p53 is produced. The specification does not provide any examples wherein an antisense to p53 produces a truncated p53 protein and results in a therapeutic outcome. The specification does not provide any specific guidance on what cells to target for a particular p53 associated disease, what antisense would be suitable for a particular disease or a particular p53 mutation, or even what p53 associated disorders would derive a therapeutic benefit from inducing a particular p53 truncation. Many of the disorders associated with p53 (eg. cancer) are due to a loss in p53 function. It is unclear how truncating p53 would provide a therapy in such cases, or at which acceptor site a truncation would provide a benefit in these cases. The specification provides no guidance with respect to these issues.

In addition to the problems associated with splice acceptor accessibility and the unpredictability of altering exon splicing, the therapeutic use of antisense oligonucleotides was generally considered unpredictable at the time the instant invention was made, and even to date (see for example Agrawal et al. (Molecular Medicine Today, Vol 6, p 72-81, February 2000), Branch, Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)) due to obstacles which include, for example, problems with delivery and *in vivo* efficacy.

Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery....Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

The field of antisense, to date, does not provide guidelines by which antisense can be routinely delivered to generally any cell type *in vivo* (whole organism) at a concentration effective to result in a predictable therapeutic effect. The specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver antisense targeted to p53 acceptor site to generally any target cell or tissue *in vivo* (whole organism) at a concentration

effective to provide a therapeutic outcome for the broad range of p53 associated diseases encompassed by the claims.

In order to practice the invention claimed, one skilled in the art would need to undergo undue trial and error experimentation, beyond the teachings of the instant specification. The quantity of undue experimentation would include the determination of what specific diseases and conditions can be treated by a particular p53 truncation, what specific cells to target with a particular p53 antisense for the treatment of a particular disease or condition, and how to specifically deliver antisense to a target cell *in vivo* (whole organism) at a concentration effective to result in a truncated p53 coding sequence. It would require the determination of splice acceptor sites and cryptic acceptor sites in eukaryotic p53 genes and the determination of what sites to target for a particular condition or p53 mutation. It would require the determination of how to induce a particular truncation, for example, what antisense sequences would produce a truncation rather than a non-sense p53 or inhibition of p53 expression. Given the art recognized unpredictability of the therapeutic application of antisense *in vivo* (whole organism), this determination would not be routine and would require undue trial and error experimentation. The guidance in the specification is minimal and general, such that even in vitro (cell culture) it would require undue experimentation to determine splice acceptor sites and antisense to produce a p53 truncation. For example, even the one described embodiment, SEQ ID NO:35, is unpredictable, for example, as to whether it would inhibit expression of

p53 given the start site proximity, or if the truncation competent sites would be favored.

Therefore, due to the broad scope of the methods claimed, including the therapeutic methods contemplated by the specification, the state of the art of antisense, the level of unpredictability of *in vivo* (whole organism) delivery of antisense and therapeutic methods, the lack of specific guidance for the *in vivo* (whole organism) application of antisense methods, the lack of guidance on acceptor sites and cryptic sites and the lack of working examples, one skilled in the art would not be able to practice the methods of claims 23-33 and 38 without undue trial and error experimentation.

Allowable Subject Matter

Claim 18 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. A morpholino oligonucleotide consisting of SEQ ID NO: 35 is free of the prior art and would be useful to inhibit the expression of p53 in a cell in culture, for example, possibly acting as a traditional antisense.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone

number is (703) 308-7523. The examiner can normally be reached on Monday-Thursday 8:30-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
January 29, 2003